

Excess all-cause mortality before age 30 in childhood onset type 1 diabetes: data from the Brecon Group Cohort in Wales

Diana R Wasag,¹ John W Gregory,² Colin Dayan,³ John N Harvey,¹ on behalf of the Brecon Group

¹Diabetes Research Group, Wrexham Academic Unit, Bangor University, Wrexham, UK
²Division of Population Medicine, Cardiff University, Cardiff, UK

³Department of Experimental and Molecular Medicine, Cardiff University, Cardiff, UK

Correspondence to

Professor John N Harvey, Department of Experimental and Molecular Medicine, Cardiff University, Gladstone Centre, Maelor Hospital, Wrexham LL13 7TD, UK; johnnharvey@btinternet.com

Received 24 December 2016

Revised 12 July 2017

Accepted 14 July 2017

Published Online First

31 August 2017

ABSTRACT

Background Long-term outcomes in young people with type 1 diabetes continue to be of interest, and may help evaluate the effects of changes to the clinical care of children that have occurred in recent decades.

Aims To identify mortality and its causes before age 30 years in patients developing type 1 diabetes before age 15 years.

Methods Since 1995, paediatricians in Wales have compiled a prospective register of incident cases of type 1 diabetes occurring before age 15 years in Wales (the Brecon Cohort). Their subsequent mortality rates were compared with mortality in the general populations of Wales and England using the patient-years exposure method. Causes of death were ascertained from death certificates and from clinicians.

Results The standardised mortality ratio for young people with type 1 diabetes in Wales was 2.91 with no clear evidence of improvement or worsening of mortality risk over time. Most deaths occurred between ages 15 and 30 years although at a slightly younger age than in the general population. There were more deaths with increasing age at diagnosis of diabetes. Ketoacidosis remains the most common cause of death before age 30 years. Hypoglycaemia was difficult to ascertain with certainty but also caused some deaths. In this age group, chronic complications of diabetes were not a cause of mortality.

Conclusions Despite the developments in clinical care in recent years, the mortality risk for people developing type 1 diabetes in childhood remains high in young adult life before the onset of chronic complications.

INTRODUCTION

Overall mortality rates among people with young onset type 1 diabetes (T1D) have reduced in more recent cohorts. So in people with 30 years duration of diabetes, the standardised mortality ratio (SMR) reduced from 9.3 in those diagnosed from 1965 to 1969, to 5.6 in those diagnosed between 1975 and 1979 in Pennsylvania.¹ Similarly in Japan, patients with 35 years duration of diabetes over the same time period showed a reduction in SMR from 10.7 to 6.6.² After 27 years of follow-up in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications trial, mortality in the tightly controlled group was not significantly different from the general US population whereas the conventionally treated group had an SMR of 1.31.³ Thus, glycaemic control is

What is already known on this topic?

- ▶ Individuals with young onset type 1 diabetes have an increased mortality.
- ▶ Mortality has reduced in older patients, probably due to less diabetic nephropathy and associated cardiovascular disease.
- ▶ Surveys have shown diabetic ketoacidosis to be a leading cause of death.

What this study adds?

- ▶ A near threefold excess mortality persists with no clear evidence of change over time in this age group (before age 30) when compared with other surveys.
- ▶ Before age 30, the excess mortality is not due to nephropathy and microvascular complications.
- ▶ Ketoacidosis remains the leading cause of death in these patients. Hypoglycaemia also contributes to mortality.

a major factor. These studies where the population is defined by long duration of diabetes find chronic complications of diabetes to be the main cause of death, particularly nephropathy and associated cardiovascular disease.⁴ However, it has been found that young people with T1D show increased mortality rates even before the onset of chronic complications.^{5 6} This remains a major concern. The intention in the current analysis was to assess mortality and its causes in younger patients before age 30 years in a cohort followed from diagnosis of T1D in Wales and, by comparison with previous studies, assess whether there is any evidence of improvement in the mortality rate.

We report (1) the current SMR among young patients with T1D in Wales and assess trends, (2) review the specific causes of death, (3) determine risk factors which might be associated with premature deaths such as age at diagnosis, gender, socioeconomic background, having a parent with diabetes and size of centre undertaking diabetes management. Identification of diagnoses and risk factors associated with mortality may offer the possibility of better targeted management and preventative strategies.



CrossMark

To cite: Wasag DR, Gregory JW, Dayan C, *et al.* *Arch Dis Child* 2018;**103**:44–48.

SUBJECTS AND METHODS

We analysed records of all individuals reported by paediatricians diagnosed with T1D before the age of 15 years while living in Wales at the time of diagnosis (the Brecon Cohort). This consisted of data on 3642 individuals, born between 1979 and 2014 and diagnosed between 1981 and 2015, followed up for a total of 42 801 patient-years of diabetes (mean follow-up 11.8 years). Ascertainment has been assessed on two occasions using a two-source capture-recapture model with data from paediatricians and primary care. Ascertainment of cases was 98.5% in those diagnosed from 1995 to 2005 and on a second assessment 98.1% from 1995 to 2012. For cases diagnosed between 1990 and 1994 ascertainment was 88.6%.

Deaths (n=30) were identified by the NHS Wales Informatics Services. Cause of death was determined for the majority of patients from the death certificate supplied by the General Register Office and/or from information provided by the responsible clinician. Cause of death was established for all cases except one. We used midyear estimates of population size and mortality obtained from the Office of National Statistics (ONS). Reference population sizes and numbers of deaths used were the mean of years 2010–2014. For the comparison of age at death in the diabetic cohort with the general population, the mean number of deaths in the population of Wales at each age from 2001 to 2015 was used.

For the purpose of investigating predictors of mortality, socioeconomic status was calculated based on the postcode registered at a time of diagnosis and converted into the Welsh Index of Multiple Deprivation, based on the 2010 Census using GeoConvert software (GeoConvert, UK). Clinic centre size was assessed as the annual mean number of newly diagnosed individuals with T1D before age 15 years between 2002 and 2013 at that centre. Family history was a dichotomous variable based on a history of diabetes in either parent at the time of the child's diagnosis.

Statistical analysis

SMRs based on death from all causes were calculated for ages 1–5 years and then 5-year age groups up to age 30 years comparing the mortality rate in our cohort with annual age-specific rates in Wales and England separately. We excluded exposure before age 1 year since this includes deaths in the reference population due to congenital conditions and prematurity which those who live to develop diabetes at an older age are by definition not exposed to. Mortality rates in the Brecon Cohort were defined as deaths per patient-years of exposure to diabetes in that 5-year age group. Exposure was calculated as length of time from diagnosis (or from age 1 year for the few diagnosed before age 1 year) until date of death, date an individual moved away from Wales, 30th birthday or the date of analysis (25 July 2015), whichever occurred first. In our cohort, 7.7% had reduced follow-up due to emigration from Wales. For calculation of the overall SMRs, we used the mortality rate in the Brecon Cohort age standardised to the population distribution of Wales.

The relationship between mortality (numbers of deaths per year) in the Brecon Cohort and age at death was assessed by Spearman correlation. Associations of sociodemographic factors with mortality over time in the diabetic cohort were assessed using Cox proportional hazards analysis. The risk factors modelled were socioeconomic status, size of centre involved in diabetic care, age at diagnosis of diabetes, parental history of any diabetes and gender. Those who died prematurely were compared with the remainder at age 30 or when censored as above. The proportionality assumption was assessed as met by

Table 1 Number of deaths and SMR relative to the population of Wales tabulated according to age at death

Age group (years)	Person-years	Number of deaths		SMR	95% CI
		Observed	Expected		
1–5	1718	1	0.243	4.1	0.1 to 23.0
5–10	6423	0	0.541	0	0 to 15.2
10–15	11 817	2	1.17	1.7	0.2 to 6.2
15–20	11 508	11	3.08	3.6	1.8 to 6.4
20–25	7479	10	3.21	3.1	1.5 to 5.7
25–30	3857	6	2.18	2.8	1.01 to 6.0

SMR, standardised mortality ratio.

analysis of Kaplan-Meier and log minus log survival plots for each covariate. Statistical analysis was undertaken using SPSS V.22.

Approval was obtained from the All Wales Research Ethics committee for this database and its use for observational analyses. Patients or guardians give written consent for their data to be used for research purposes.

RESULTS

Thirty deaths before age 30 years were identified in this cohort of people diagnosed with T1D before age 15 years. The all-cause mortality between ages 1 and 30 years was 2.91 times higher than expected: SMR 2.91 (95% CI 1.96 to 4.15) in comparison to the same age group mortality rates in Wales. The SMR was 3.40 (2.30–4.86) relative to England. Looking at the individual age groups, mortality was significantly higher from age 15 to 30 years (table 1). The numbers of deaths per year increased with increasing age ($\rho=0.46$, $p=0.01$). Deaths before age 15 years were few. Age at death in those with diabetes compared with deaths before age 30 years in the whole Welsh (predominantly non-diabetic) population is shown in figure 1. Median survival time to death was to age 20.1 (SE 0.8) years in those with diabetes and to 22.5 (SE 0.5) years in those dying in the general population of Wales ($p=0.017$, log rank test).

Cause of death is listed in table 2. The most common cause of death was ketoacidosis (n=9). Hypoglycaemia is difficult to ascertain with certainty because confirmation (eg, by measurement of vitreous glucose concentration) is rarely sought at autopsy. The six deaths we felt likely to be the result of hypoglycaemia were based on death certification and the views of the responsible physicians and diabetic nurses. There were two fatal road traffic accidents, one as driver and one as pedestrian where the clinic staff providing care suspected hypoglycaemia. If deaths due to ketoacidosis and hypoglycaemia were to be excluded, the SMR would be 1.39 (0.78–2.29).

Based on four cases, the SMR for death by suicide in this cohort versus the population of Wales was 2.1 (0.57–5.70). Major congenital heart disease occurred in the context of Down syndrome in two cases.

Age at diagnosis of diabetes predicted mortality in this cohort: the relative hazard per additional year of age 1.16 (1.05–1.28) $p=0.005$. There was no statistically significant association of mortality with socioeconomic status: relative hazard 1.0 (1.0–1.0) $p=0.13$, positive parental history of diabetes: relative hazard 1.24 (0.30–5.22) $p=0.77$ or size of centre involved in diabetic care: relative hazard 1.0 (0.94–1.07) $p=0.83$. In our population, more deaths were observed in men than women (21 vs 9). The relative hazard for men was 2.07 (0.95–4.53) $p=0.068$. However, this gender difference

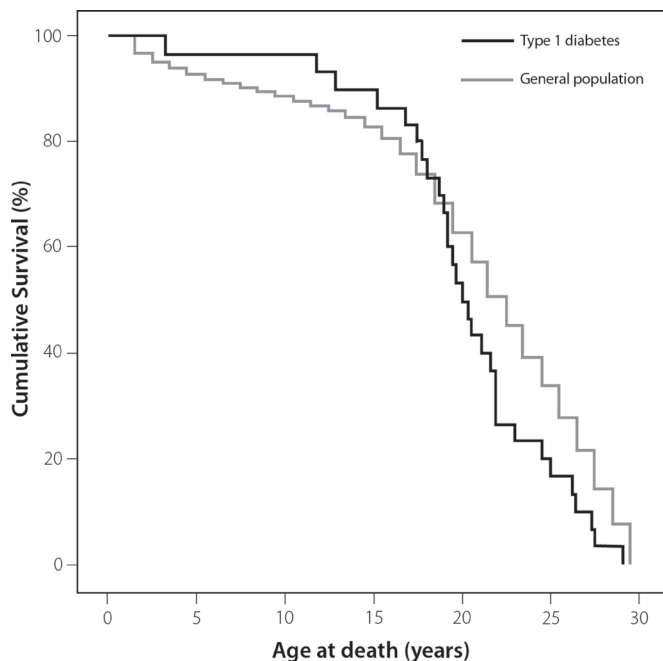


Figure 1 Survival probability for young onset type 1 diabetic patients with death before age 30 compared with individuals dying before age 30 in the whole population of Wales. Death in the diabetic cohort occurred earlier with median survival to age 20.1 (SE 0.8) years vs 22.5 (SE 0.5) in the reference population ($p=0.017$, log rank test).

is not dissimilar from the Welsh population as a whole where from 2010 to 2014 in people aged 1–30 there were 206.0 deaths per year in men and 95.4 in women. Thus, our cohort had an SMR of 2.80 (1.73–4.28) in men and 3.01 (1.37–5.70) in women.

The Brecon Group register also identified nine deaths before age 30 years over this period in patients with non-T1D. The causes of death were cystic fibrosis (seven), Alstrom syndrome (one) and meningococcal sepsis during treatment for acute

Table 2 The causes of death. One patient had death certified due to 'Myocardial infarction (stented) and diabetic ketoacidosis' and appears in both categories. One patient had death certified due to 'Insulin overdose' and appears in the hypoglycaemia and suicide categories

Cause of death	n	Age at death Years (median and range)	Duration of diabetes Years (median and range)
Ketoacidosis	9	22 (18–28)	11 (5–13)
Likely hypoglycaemia	6	21 (17–27)	11 (4–16)
'Dead in bed' syndrome	2	21 (19–22)	8 (7–9)
Suicide	4	20 (19–27)	16 (7–16)
Large vessel disease	2	22 (20–23)	10 (9–10)
Sepsis	2	23 (20–25)	11 (9–14)
Congenital heart disease (Down syndrome)	2	7 (3–12)	4 (0–7)
Complications of transplantation	2	25 (21–29)	18 (9–27)
Ulcerative colitis	1	19	12
Road accident (father driving)	1	15	13
Unknown cause	1	13	1

lymphoblastic leukaemia in a child with steroid-induced diabetes.

DISCUSSION

The Welsh NHS informatics database is linked to the ONS and would be expected to have complete ascertainment of deaths. Ascertainment of cases of T1D in our database was high from 1990 such that this can be considered a population-based survey. The annual incidence of T1D before age 15 years in Wales has been approximately 29 cases per 100 000 population since 2000 (unpublished data).

The overall SMR before age 30 years was 2.91. This is very similar to a recent estimate of 2.96 in Northern Ireland.⁷ Previously reported SMRs were 2.47 before age 34 years from Yorkshire 1978–1995⁵ and 2.3 before age 20 years from an England, Wales and Scotland survey.⁶ It would therefore seem that the mortality rate in this patient group has not decreased and may in fact have increased. However, the Yorkshire analysis did not exclude the under age 1 population where there are significant numbers of deaths due to prematurity and major congenital malformations in the reference population.⁵ These are not seen in the diabetic population because patients have by definition survived this age period to develop diabetes at an older age. This is a bias which causes an underestimate of the SMR. The National Survey from Oxford relied on diabetes being mentioned on the death certificate which allows that death from other causes (eg, suicide) may have been missed giving a low estimate for SMR.⁶ Also, the National Survey reported deaths up to age 20 years where we find a lower mortality rate. Thus, it is not necessarily the case that mortality in the UK has increased in this young diabetic population. Recent data from Western Australia found an SMR of 3.1 for mortality at ages 1–17 years and 3.3 at ages 18–38 years.^{8,9}

Our SMR was higher when the population of England was used as the reference population. This illustrates that in the general population, mortality before age 30 years is lower in England than in Wales. Mortality in those with diabetes in Wales was significantly increased from age 15 years onwards. Thus, deaths do not seem to be an immediate consequence of the diagnosis of diabetes such as ketoacidosis or due to lack of knowledge about the management of diabetes in the early years. Survival analysis comparing deaths in the Brecon Cohort with deaths before age 30 in Wales as a whole showed that the deaths in the diabetic cohort did occur approximately 2 years earlier than deaths before age 30 in the reference population. A steep drop in survival probability was seen between ages 17 and 22, the age of adolescence and transition to adult services. Mortality was associated with increasing age at diagnosis, that is, those diagnosed in teenage years were more at risk of death than those who developed diabetes younger even though mortality occurred some years later. Given that behavioural factors play a role in some of the deaths (ketoacidosis, suicide), there is the implication that those diagnosed in the teenage years are less well adjusted to their condition than younger onset patients. This has its maximum effect at ages 17–22 years. The results argue for greater use of psychological interventions in young adult patients with T1D.¹⁰

We found more deaths in men than women (21 v 9). This is similar to the findings in Yorkshire.⁵ Despite the fact that the majority of our deaths were diabetes related, the male excess is similar to that found in deaths in the general population in that age group. Thus, the SMR in women was marginally but not significantly greater. In Western Australia, Cooper *et al* found a

higher SMR in women dying at ages 18–38 years.⁹ The EURO-DIAB analysis also found a higher SMR in women: 2.7 v 1.8.¹¹ Surveys which include older patients with longer follow-up tend to have more male mortality because of the development of nephropathy which is more common in men.¹²

The most common cause of death among our cohort was ketoacidosis, as shown in other studies of young people with diabetes.^{5,6,8} Ketoacidosis in the paediatric age range is known to predispose to cerebral oedema.⁶ Behavioural factors including eating disorders are often implicated when ketoacidosis occurs in individuals with known diabetes.¹³ In other surveys, deaths due to hypoglycaemia have also been identified but less frequently than ketoacidosis, as here.^{5,6} Further calculation indicated that if mortality from these acute complications of diabetes could be completely prevented then only a small increase in the diabetic population (not significant in our analysis) would remain. We recorded two cases of the ‘Dead in bed’ syndrome. This is a comparable prevalence to other surveys of this phenomenon.^{14,15}

Our data suggested a doubling of suicides compared with the reference population although the results were not statistically significant. Small excesses of deaths due to accidents and suicide have been previously reported.^{9,11} These deaths might be a result of the psychological challenges faced by young people with diabetes. Identification of high-risk groups offers the potential to prevent suicide: 1 in 10 completed suicides have a chronic medical illness.¹⁶

Large vessel disease such as myocardial infarction and ischaemic stroke is a rarity before age 30 years in the general population but our results indicate it contributes to mortality in young patients with T1D. T1D is associated with excess cardiovascular morbidity and mortality. An excess of risk factors in these patients has been reported.¹⁷ Moreover, adverse changes in cardiovascular function, arterial compliance and atherosclerosis can be present during adolescence in people with T1D.¹⁸ We have identified deaths but more non-fatal disease will be present in this population. Screening programmes for large vessel disease in young people with diabetes need to be developed.

No data have been published in the UK regarding the association with socioeconomic status, or having a parent with diabetes, as possible risk factors for premature mortality. We found no relationship between mortality and socioeconomic status derived from postcode at diagnosis. In a systematic review including studies from many nations, there was no relationship between mortality and gross domestic product per head of population but a reduction in mortality with increased expenditure on healthcare.¹⁹ Higher mortality rates among individuals from lower socioeconomic background have been reported in Western Australia.⁹

Some argue that larger centres can provide better care; others that smaller centres offer more personal support. As far as it influences mortality before age 30 years, we found no difference in rates in those diagnosed in smaller units versus larger centres.

Although the present study has clear strengths, a large cohort, population-based case ascertainment and analysis of risk factors for premature mortality, it also has limitations. The numbers of events are small. Limited clinical information was available regarding the cause of death as we had no access to individual clinical records. Despite these limitations, this study identifies persistent premature mortality among young people with T1D.

CONCLUSIONS

Young people with T1D have a persistent, nearly threefold higher risk of mortality before age 30 years compared with the general population, with the 15 to 30-year-old age group at greatest risk. Before age 30, we found no deaths due to diabetic nephropathy

and little evidence of microvascular disease contributing to death. The continuing predominance of mortality due to ketoacidosis, especially in patients who developed diabetes in later childhood, suggests the need to target behavioural factors including during and after the transition to adult clinics. Psychological input is required for some patients. Consideration of who might be at risk of suicide is important. In addition, the frequency of ketoacidosis as a cause of death indicates that treatments able to preserve residual beta cell function in the first 10 years after diagnosis might reduce death rates in this group. Physicians need to keep in mind that ischaemic heart disease or stroke due to large vessel disease can present before age 30 years in this patient population.

Contributors DRW and JNH collected and analysed the data and wrote the first draft of the manuscript. JNH and JWG are responsible for the database from which these data are taken. JWG and CD reviewed and commented on the manuscript. JNH prepared the final and revised version. The authors jointly take responsibility for the manuscript. The Brecon Group (which comprises all paediatricians in Wales with an interest in Diabetes and Endocrinology) is also contributor to this report.

Funding None declared.

Competing interests None declared

Patient consent Parental/guardian consent obtained.

Ethics approval Wales Multicentre Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Secrest AM, Becker DJ, Kelsey SF, *et al.* All-cause mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes: the Allegheny County type 1 diabetes registry. *Diabetes Care* 2010;33:2573–9.
- 2 Morimoto A, Onda Y, Nishimura R, *et al.* Cause-specific mortality trends in a nationwide population-based cohort of childhood-onset type 1 diabetes in Japan during 35 years of follow-up: the DERI Mortality Study. *Diabetologia* 2013;56:2171–5.
- 3 Epidemiology of Diabetes Interventions and complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. *Diabetes Care* 2016;39:1378–83.
- 4 Secrest AM, Becker DJ, Kelsey SF, *et al.* Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes. *Diabetes* 2010;59:3216–22.
- 5 Warner DP, McKinney PA, Law GR, *et al.* Mortality and diabetes from a population based register in Yorkshire 1978–93. *Arch Dis Child* 1998;78:435–8.
- 6 Edge JA, Ford-Adams ME, Dunger DB, *et al.* Causes of death in children with insulin dependent diabetes 1990–96. *Arch Dis Child* 1999;81:318–23.
- 7 Patterson CC, Cardwell CR, McCance DR, *et al.* Mortality in patients diagnosed with diabetes during childhood in Northern Ireland, UK. *Pediatr Diabetes* 2013;14:40. Abstract 050.
- 8 O’Grady MJ, Delaney J, Jones TW, *et al.* Standardised mortality is increased three-fold in a population-based sample of children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2013;14:13–17.
- 9 Cooper MN, de Klerk NH, Jones TW, *et al.* Clinical and demographic risk factors associated with mortality during early adulthood in a population-based cohort of childhood-onset type 1 diabetes. *Diabet Med* 2014;31:1550–8.
- 10 Harvey JN. Psychosocial interventions for the diabetic patient. *Diabetes Metab Syndr Obes* 2015;8:29–43.
- 11 Patterson CC, Dahlquist G, Harjutsalo V, *et al.* Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. *Diabetologia* 2007;50:2439–42.
- 12 Maric C, Forsblom C, Thorn L, *et al.* On behalf of the FinnDiane Study Group. Association between testosterone, estradiol and sex hormone binding globulin levels in men with type 1 diabetes and nephropathy. *Steroids* 2010;75:772–8.
- 13 Peveler RC, Bryden KS, Neil HA, *et al.* The relationship of disordered eating habits and attitudes to clinical outcomes in young adult females with type 1 diabetes. *Diabetes Care* 2005;28:84–8.
- 14 Secrest AM, Becker DJ, Kelsey SF, *et al.* Characterizing sudden death and dead-in-bed syndrome in type 1 diabetes: analysis from two childhood-onset type 1 diabetes registries. *Diabet Med* 2011;28:293–300.
- 15 Koltin D, Daneman D. Dead-in-bed syndrome - a diabetes nightmare. *Pediatr Diabetes* 2008;9:504–7.

- 16 Cole-King A, Green G, Gask L, *et al*. Suicide mitigation: a compassionate approach to suicide prevention. *Advances in Psychiatric Treatment* 2013;19:276–83.
- 17 Kummernes SJ, Drivvoll AK, Dahl-Jorgensen K, *et al*. Increased cardiovascular disease risk factors, especially in girls: a nationwide, population-based study of children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2013;14:23. abstract O11.
- 18 Snell-Bergeon JK, Nadeau K. Cardiovascular disease risk in young people with type 1 diabetes. *J Cardiovasc Transl Res* 2012;5:446–62. [Erratum: *J Cardiovasc Transl Res*. 2012; Aug,5(4): 554].
- 19 Morgan E, Cardwell CR, Black CJ, *et al*. Excess mortality in type 1 diabetes diagnosed in childhood and adolescence: a systematic review of population-based cohorts. *Acta Diabetol* 2015;52:801–7.